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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/600,116	06/20/2003	Pier Andrea Borea	58045-U1(46453)	8955

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EXAMINER	
GRAFFEO, MICHEL	
ART UNIT	**PAPER NUMBER**
1614	

DATE MAILED: 03/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/600,116	BOREA ET AL.	
	Examiner	Art Unit	
	Michel Graffeo	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-27 is/are pending in the application.

4a) Of the above claim(s) 1-22,26 and 27 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 23-25 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 12 Jan 04.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Action

Claims 23-25 are pending and examined.

Election/Restrictions

Claims 1-22 and 26-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 14 November 2005.

Applicant's election with traverse of claims 23-25 in the reply filed on 14 November 2005 is acknowledged. The traversal is on the ground(s) that a search of both inventions would not be a serious burden on the Examiner. This is not found persuasive because the claims are of differing scope, have different end point, patient populations and e.g., treatment regfimes. For example, the invention of Group I includes a generic compound and lacks the limitation of a method comprising a adenosine-5'-triphosphate depleting agent. Thus, the search of any one invention would not have resulted in a complete search of any on other invention and therefore the search burden is established.

The requirement is still deemed proper and is therefore made FINAL.

Claim Objections

Claims 24-25 are objected to because of the following informalities: Since claims 24-25 include a depleting agent, it appears that claims 24-25 are dependent upon claim 23 and have been interpreted and examined as such. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while arguably being enabled for the enhancing of certain chemotherapies comprising the adenosine-5'-triphosphate depleting agents enabled in US Patent No. 6,210,917 (see below) and the A3 receptor antagonists enabled in US Patent No. 6,066,642 (see below) does not reasonably provide enablement for a method of enhancing the chemotherapeutic treatment of cancer comprising any and all adenosine A3 receptor antagonists, any and all depleting agents and any and all chemotherapeutic agents for any and all cancers which are MDR and P-glycoprotein dependent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2nd 1400 (Fed. Cir. 1988) as to undue experimentation.

The factors include:

1) the nature of the invention;
2) the breadth of the claims;
3) the predictability or unpredictability of the art;
4) the amount of direction or guidance presented;
5) the presence or absence of working examples;
6) the quantity of experimentation necessary;
7) the state of the prior art; and ,
8) the relative skill of those skilled in the art.

Each factor is addressed below on the basis of comparison of the disclosure, the claims and the state of the art in the assessment of undue experimentation.

1) the nature of the invention; the invention is directed to a method of enhancing the chemotherapeutic treatment of cancer comprising an adenosine A3 receptor antagonists, a depleting agents and a chemotherapeutic agents wherein the cancers are MDR and P-glycoprotein dependent.

2) the breadth of the claims; the scope of the method claims includes the method of enhancing the chemotherapeutic treatment of cancer comprising any and all adenosine A3 receptor antagonists, any and all depleting agents and any and all chemotherapeutic agents for any and all cancers which are MDR and P-glycoprotein dependent.

3) the predictability or unpredictability of the art; no compounds are recited in the claims and therefore contemplate compounds not recited in the prior art.

Consequently, there is are no disclosures which would enable one of ordinary skill in the art to identify patients, predict dosages and routes of administration for example in each case wherein the compound are to be used for such a broad possibility of indications especially where as here, there is no indication of any commonality of mechanism of action for the recited drug in the claimed diseases/conditions. None of the examples either single or collectively demonstrate each of the treatments as successful.

4) the amount of direction or guidance presented; the specification does not provide any guidance in terms a method of enhancing the chemotherapeutic treatment of cancer comprising any and all adenosine A3 receptor antagonists, any and all depleting agents and any and all chemotherapeutic agents for any and all cancers which are MDR and P-glycoprotein dependent. Therefore, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. See, e.g., Chiron Corp. v. Genentech Inc., 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004) ("Nascent technology, however, must be enabled with a specific and useful teaching.' The law requires an enabling disclosure for nascent technology because a person of ordinary skill in the art has little or no knowledge independent from the patentee's instruction. Thus, the public's end of the bargain struck by the patent system is a full enabling disclosure of the claimed technology." And, in this case, since compounds contemplated in the scope of the claims may be novel, there is a lack

of predictability. The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability.

The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required. A single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements. In re Vickers, 141 F.2d 522, 526-27, 61 USPQ 122, 127 (CCPA 1944); In re Cook, 439 F.2d 730, 734, 169 USPQ 298, 301 (CCPA 1971). However, in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. In re Soll, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and

physiological activity). See also In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). See for example, Ohana et al. Inhibition of primary colon carcinoma growth and liver metastasis by the A3 adenosine receptor agonist CF101. British Journal of Cancer (2003) 89, 1552-1558 which teaches on page 1555 that A3 receptor agonists possess anticancer properties and see also Fishman et al. Adenosine acts as an inhibitor of lymphoma cell growth: a major role for the A3 adenosine receptor. European Journal of Cancer 36 (2000) 1452-1458 which also teaches that adenosine has anti cancer efficacy, both which are contradictory to the claims in the instant Application and which provide a showing that an undue burden of experimentation would be placed on one of ordinary skill in the art to make and use the invention not only at the time of filing, but currently as well.

Finally, no *in vivo* experiments are disclosed in the specification and the specification does not teach a single species for use in the above method claims. In particular, the Specification does not teach or show any experimental evidence (particularly *in vivo* experimental evidence or in vitro evidence and explanation of correlation to *in vivo* efficacy) for a method that comprises an adenosine A3 receptor antagonist and a depleting agent.

5) the presence or absence of working examples; no working examples are provided in the specification. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely

with the degree of unpredictability of the factors involved". See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

6) the quantity of experimentation necessary; the quantity of experimentation would be an undue burden to one of ordinary skill in the art and amount to the trial and error type of experimentation. Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention and unpredictability of the use of A3 receptor antagonists for treating cancer, and the lack of working examples regarding the activity as claimed, one skilled in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

In consideration of each of factors 1-6, it is apparent that there is undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 23-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6,066,642 to Jacobson et al. in view of Baraldi et al. Pyrozolo[4,3-e]-1,2,4-triazolo[1,5-cl-pyrimidine derivatives as highly potent and selective human A3 adenosine receptor antagonists. Journal of Medicinal Chemistry. Vol 42 (1999) 4473-4478 and further in view of US Patent No. 6,210,917 to Carson et al. (cited to show the status in the art).

Jacobson et al. teach the use of adenosine A3 receptor antagonists in the killing of cancer cells (in current claims 23-25; see col 63 Example 31).

Jacobson et al. do not specifically teach the use of MRE3008F20.

Baraldi et al. teach that MRE3008F20 is a adenosine A3 receptor antagonists (in current claims 23-25; see page 4476 compound #7).

Jacobson et al. and Baraldi et al. do not teach the combination of an adenosine A3 receptor antagonists with an adenosine-5'-triphosphate depleting agent.

Nonetheless, combining agents which are known to be useful as chemotherapies individually into a singe composition useful for the very same purpose is prima facie obvious. See In re Kerkhoven 205 USPQ 1069. The fact that a first component is not chemically related to a second component, but where each as the same utility, does not detract from the general presumption of the obviousness of combining the two. In re Linder, 457 F.2d 506, 507 (CCPA 1972). (Holding that it would have been obvious to have combined two known dispersants, since one skilled in the art would have expected a mixture of dispersants to also be a dispersant). Moreover, picking and choosing individual components from several references, each of which discloses a plurality of components, is permissible where each component has the same individual utility. In re Dial, 326 F. 2d 430, 432 (CCPA 1964). (Holding that it would have been obvious to have combined four individual stabilizers from three different references, absent evidence in the record that Applicant's particular combination of stabilizers was more effective at inhibiting decomposition than any single member of that combination).

Since it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose, the idea of combining an adenosine A3 receptor antagonist with an adenosine-5'-triphosphate depleting agent flows logically from their having been individually taught in the prior art. To that end, Carson et al. teaches a combination therapy comprising an adenosine-5'-triphosphate depleting agent to treat cancers that are MDR (in current claims 23-25; see Abstract).

One of ordinary skill in the art would have been motivated to combine the above references and as combined would teach the invention as claimed. One of ordinary skill in the art would have been motivated to combine the above references because a known adenosine A3 receptor antagonist such as MRE3008F20 would be obvious to one skilled in the art over Jacobson et al. which teaches the use of adenosine A3 receptor antagonist to treat cancer. Further, the combination of anticancer agents in a multivalent therapy is obvious which provides the motivation to combine Carson et al. Thus, the combined references teach and make prima facie obvious how to use the claimed invention at the time that it was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

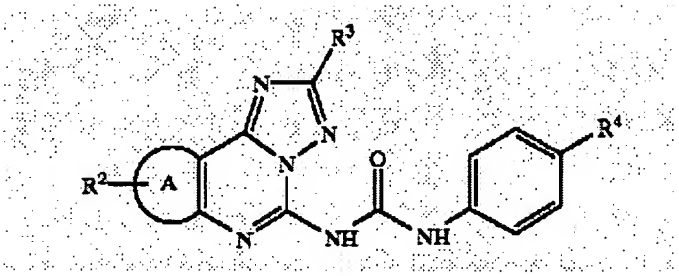
Claims 23-25 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 23-25 of copending Application No. 10/603406.

The subject matter claimed in the instant application is fully claimed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: a method of synergistically enhancing the chemotherapeutic treatment of cancer expressing adenosine A3 receptors comprising administering to a mammal in need thereof an effective amount of a high affinity adenosine A.sub.3 receptor antagonist and a adenosine-5'-triphosphate depleting agent either prior to or during administration of a chemotherapeutic cancer agent wherein the cancer has multi-drug resistance that is P-glycoprotein dependent..

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 23-25 rejected on the ground of nonstatutory double patenting over claims 1-8 of U. S. Patent No. 6,921,825 since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent.

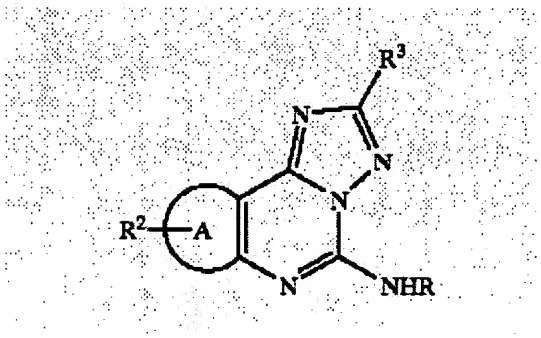
The subject matter claimed in the instant application is fully claimed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows: a compound having the following formula:



Although the patent claims are directed to a composition, the current claims are directed to the use of a class of compounds in which the patent compounds are part of and therefore, would be used to practice the instant method claims.

Claims 23-25 rejected on the ground of nonstatutory double patenting over claims 1-12 of U. S. Patent No. 6,407,236 since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent.

The subject matter claimed in the instant application is fully claimed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows: a compound having the following formula:



Although the patent claims are directed to a composition, the current claims are directed to the use of a class of compounds in which the patent compounds are part of and therefore, would be used to practice the instant method claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michel Graffeo whose telephone number is 571-272-8505. The examiner can normally be reached on 9am to 5:30pm Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

25 February 2006
MG

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